LETTERS TO THE EDITOR

Scope
Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation
Letters should be:
- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors.

They may contain short tables or a small figure. **Please send a copy of your letter on disk**. Full instructions to authors appear in the January 1997 issue of *Heart* (page 89).

Hyperhomocysteinaemia and premature coronary artery disease in the Chinese

SIR,—We were interested by the study by Lolin and colleagues.[1] The Chinese patients with premature coronary artery disease had higher concentrations of folate in serum and erythrocytes, and higher serum vitamin B_{12} than healthy control subjects. There was not a significant difference in prevalence of fasting hyperhomocysteinaemia; however, there was a significantly higher prevalence of hyperhomocysteinaemia following methionine loading in patients versus controls. There was a significant difference in fasting and post-methionine load plasma total homocysteine (tHcy) in patients compared with control subjects ($P = 0{\cdot}004$ and $P = 0{\cdot}003$).

Hyperhomocysteinaemia may emerge due to genetic factors, for instance from deficiency of the enzyme cystathionine β synthase (CBS), which participates in a transsulphuration pathway, or from thermolabile or mutant enzyme methylenetetrahydrofolate reductase (MTHFR) which synthesises 5-methyltetrahydrofolate, or from inborn errors of cobalamin transport and metabolism. Lower concentrations of vitamins B_{12}, B_6, B_2, cofactor form flavin adenine dinucleotide (FAD), or folate in serum or plasma may also be associated with hyperhomocysteinaemia. Vitamins B_{12}, B_6, and B_2 are coenzymes for enzymes methionine synthase, CBS, and MTHFR, respectively. 5-Methyltetrahydrofolate is a methyl donor for methylation of homocysteine into methionine. Deficiency of these vitamins in blood may occur because of dietary or environmental factors.[2]

Miller and colleagues[3 4] have indicated that vitamin B_6 deficiency in humans or rats may not be associated with fasting hyperhomocysteinaemia. Fasting plasma tHcy concentrations in vitamin B_6 deficient rats were not significantly different from those in control rats; however, the folate deficient rats had plasma tHcy concentrations nearly 10-fold higher than control rats ($P = 0{\cdot}001$). During methionine loading, vitamin B_6 deficient rats exhibited a dramatic elevation of plasma tHcy concentrations which persisted for four hours or longer ($P < 0{\cdot}001$). Folate deficient rats did not show any significant increase in plasma tHcy.[3 4]

My colleagues and I have shown that serum folate and vitamin B_{12} concentrations had significant influence on fasting plasma tHcy concentrations; however; the influence of vitamin B_6 on fasting plasma tHcy was weak, probably due to smoking.[5]

These findings may indicate that homocysteine response during methionine loading may be different for folate or vitamin B_6 deficiency. Folate deficiency may be associated with fasting hyperhomocysteinaemia. Methionine loading test may be used to uncover post-load hyperhomocysteinaemia which may be associated with deficiency of vitamin B_6 or heterozygote deficiency of CBS.

Therefore, it may be interesting to measure concentrations of vitamin B_6 in plasma or whole blood to investigate a potential role of vitamin B_6 in the development of hyperhomocysteinaemia in the Chinese patients. This might be important because patients with premature coronary artery disease had higher concentrations of folate in serum and erythrocytes. Measurement of vitamin B_2 in the serum from patients and control subjects may also add new information in the study.

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1 Lolin YI, Sanderson JE, Cheng SK, Chan CF, Pang CP, Woo KS, Masarei JRL. Hyperhomocysteinaemia and premature coronary artery disease in the Chinese. *Heart* 1996;**76**: 117–22.
2 Ueland PM, Refsum H, Brattström L. Plasma homocysteine and cardiovascular disease. In: Francis RB Jr, ed. *Atherosclerotic cardiovascular disease, haemostatis, and endothelial function*. New York: Marcel Dekker, 1992: 183–236.
3 Miller JW, Ribaya-Mercado JD, Russell RM, Shepard DC, Morrow FD, Cochary EF, *et al*. Effect of vitamin B-6 deficiency on fasting plasma homocysteine concentrations. *Am J Clin Nutr* 1992;**55**:1154–60.
4 Miller JW, Nadeau MR; Smith D, Selhub J. Vitamin B-6 deficiency *v* folate deficiency: comparison of responses to methionine loading in rats. *Am J Clin Nutr* 1994;**59**:1033–9.
5 Bergmark C, Mansoor MA, Swedenborg J, de Fair U, Svardal AM, Ueland PM. Hyperhomocysteinemia in patients operated for lower extremity ischaemia below the age of 50—effect of smoking and extent of disease. *Eur J Vasc Surg* 1993;7:391–6.

This letter was shown to the authors, who reply as follows:

SIR,—We thank Dr Mansoor for his helpful comments on our study, particularly on the importance of finding the causes(s) for hyperhomocysteinaemia in our subjects. His suggestions about measuring B_6 and B_2 are very welcome. They are, however, based on the observations that the incidence of post-methionine hyperhomocysteinaemia, but not of fasting hyperhomocysteinaemia, was significantly higher in patients than in controls. The number of subjects in our study was small and, though not statistically significant, there was a difference between patients and controls regarding fasting hyperhomocysteinaemia (22% *v* 4·8%, respectively). Further, the mean serum homocysteine levels were significantly higher in patients than in controls in both the fasting and post-methionine states, although the difference between the fasting levels was less striking.

Dr Mansoor pointed out the many causes for hyperhomocysteinaemia and indicated that low serum or plasma folate levels were associated predominantly with fasting hyperhomocysteinaemia, and B_6 deficiency or heterozygote deficiency of cystathionine β synthase (CBS) with post-methionine hyperhomocysteinaemia. Our study showed that in the Hong Kong Chinese, folate and B_{12} deficiencies were unlikely to be aetiologically important. This may have contributed to the relatively low incidence of, and modest fasting, hyperhomocysteinaemia. The striking response to methionine may well have been accounted for by heterozygous deficiency of CBS. Dietary deficiencies of B_6 and B_2, although possible, are less likely although we will follow the suggestions of Dr Mansoor. Both vitamins are present, among others, in poultry, meat, fish, soya bean (particularly B_6), asparagus (particularly B_2), spinach, and broccoli, all of which are eaten in abundance in this population throughout the year. A defective utilisation of these coenzymes through deficiency of CBS and the presence of the heat labile or a mutant 5-methyltetrahydrofolate reductase is, however, a distinct possibility and we are presently investigating these enzymes in our population.

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Homocysteinaemia and coronary atherosclerosis

SIR,—I read with great interest the article on hyperhomocysteinaemia and premature coronary artery disease in Hong Kong Chinese patients.[1] As suggested by the title of the accompanying editorial,[2] homocysteine has emerged as another risk factor for the development of coronary artery disease.

Homocysteine in human plasma arises solely from the breakdown of the essential amino acid methionine obtained only from dietary sources. Dietary homocysteine is complexed to various thiols, and does not appear under normal circumstances to influence plasma homocysteine.[3] The plasma concentration of homocysteine is strictly controlled and kept within a very narrow range in normal subjects, either by its degradation via cystathionine to cysteine and pyruvate, or by its remethylation to methionine.[4] Although it can be made to rise by ingestion of a very high so-called "loading dose" of methionine in normal subjects on normal diets, such postprandial increases are small, with plasma homocysteine concentrations declining rapidly to the normal range. The study by Lolin and colleagues[1] suggests that in the Hong Kong Chinese patients hyperhomocysteinaemia was associated with genetically inherited abnormalities in enzymes associated with its metabolism.

Thus, while patients with reduced concentrations of cystathionine synthase, methionine synthase, or 5,10-methylene tetrahydrofolate reductase have a widely varying biochemical outcome, they all have in common an elevated plasma homocysteine.[3] Patients with these metabolic distur-